Highly Active Antiretroviral Therapy and the Kidney: An Update on Antiretroviral Medications for Nephrologists

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Highly active antiretroviral therapy has dramatically altered the treatment and life expectancy of individuals who are infected with HIV. More than 20 antiretroviral drugs and drug combinations now are available in the United States. Nephrologists need to have an understanding of the pharmacokinetics of antiretroviral medications and the proper dosing of these medications in patients with impaired kidney function. It is also important for nephrologists to be aware of drug–drug interactions that can occur between antiretroviral medications and other medications that they may prescribe, including immunosuppressive medications that are used for renal transplantation, as this becomes more common in HIV-infected patients. Adverse reactions that affect the kidneys and cause fluid-electrolyte complications occur with certain antiretroviral agents, although most are relatively free of nephrotoxicity. This article reviews the clinical pharmacology and dosing modifications of the newer antiretroviral medications in patients with reduced kidney function; important drug–drug interactions involving these medications, particularly with other medications that are likely to be prescribed by nephrologists; and renal toxicities of antiretroviral agents.


Clinical Pharmacology and Dosing of Antiretroviral Agents in Patients with Kidney Disease

Many antiretroviral agents are eliminated at least partly by the kidneys and require dosage adjustments in patients with reduced GFR. In adjusting antiretroviral agents in HIV-infected patients with reduced GFR, it should be kept in mind that serum creatinine may be a poor marker of renal function, especially in patients with muscle wasting. Nonetheless, most dosing recommendations provided by pharmaceutical manufacturers and in the literature are based on creatinine clearance (CrCl). Also, the Cockcroft-Gault and Modification of Diet in Renal Disease (MDRD) formulas have not been validated in HIV-infected individuals. The reader is referred elsewhere for more complete information on drug dosing in patients with reduced kidney function, including those who are on hemodialysis and peritoneal dialysis (11–14). For many of these drugs, particularly the newer ones, there are only very limited reports on the effects of reduced GFR and dialysis on pharmacokinetic...
parameters. The effects of an intradialytic reduction of plasma concentrations on intracellular levels of antiretroviral agents are largely unknown. Therefore, it is not always certain that recommended dosage adjustments in patients with impaired GFR reduce toxicity and still maintain efficacy of antiretroviral therapy (13).

**Figure 1.** Replication life cycle of HIV and sites of antiretroviral drug action. HIV enters the cell by binding to CD4 and other cell surface receptors and then is internalized. This step is inhibited by fusion/entry inhibitors. HIV RNA is released from the nucleocapsid, then reverse transcriptase copies genomic RNA into unintegrated proviral DNA. This process is inhibited by nucleoside/nucleotide reverse transcriptase inhibitors (NRTI) and non-nucleoside reverse transcriptase inhibitors (NNRTI). Proviral DNA then is inserted into host cell DNA. An integrase inhibitor is undergoing clinical trials. Host genome with inserted HIV genome is transcribed into RNA, including new proviral RNA that will be packaged in new virions as viral RNA. Other RNA is translated into viral capsid and regulatory proteins. The processing of amino acid sequences involves posttranslational cleaving of polyproteins by a specific viral protease that is inhibited by protease inhibitors (PI). Finally, viral RNA is packaged in new capsid envelopes and released from the cell as newly formed intact and infectious virions. Illustration by Josh Gramling—Gramling Medical Illustration.

**Table 1.** Protease inhibitors

<table>
<thead>
<tr>
<th>Brand Name</th>
<th>Generic Name</th>
<th>Usual Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Invirase</td>
<td>Saquinavir (Hard-gel)</td>
<td>1000 mg bid with ritonavir 100 mg bid</td>
</tr>
<tr>
<td>Norvir</td>
<td>Ritonavir</td>
<td>600 mg bid</td>
</tr>
<tr>
<td>Crixivan</td>
<td>Indinavir</td>
<td>800 mg q8h</td>
</tr>
<tr>
<td>Viracept</td>
<td>Nelfinavir</td>
<td>750 mg tid or 1250 mg bid</td>
</tr>
<tr>
<td>Fortovase</td>
<td>Saquinavir (Soft-gel)</td>
<td>1200 mg tid</td>
</tr>
<tr>
<td>Agenerase</td>
<td>Amprenavir</td>
<td>1200 mg bid</td>
</tr>
<tr>
<td>Kaletra</td>
<td>Lopinavir/Ritonavir</td>
<td>lopinavir 400 mg/ritonavir 100 mg bid</td>
</tr>
<tr>
<td>Reyataz</td>
<td>Atazanavir</td>
<td>400 mg daily</td>
</tr>
<tr>
<td>Lexiva</td>
<td>Fos-amprenavir</td>
<td>1400 mg bid</td>
</tr>
</tbody>
</table>

*No dose adjustments are necessary for patients who have reduced GFR or who are on dialysis. For guidance with dosing antiretroviral combinations and dosing in highly active antiretroviral therapy (HAART)-experienced patients, refer to individual package inserts. bid, twice daily; tid, three times daily.*


**Table 2. Nucleoside/nucleotide reverse transcriptase inhibitors**

<table>
<thead>
<tr>
<th>Brand Name</th>
<th>Generic Name</th>
<th>Usual Dose</th>
<th>Dose for Reduced GFR (CrCl)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Emtriva</td>
<td>Emtricitabine</td>
<td>200 mg/d</td>
<td>30 to 49 ml/min: 200 mg q48h</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>15 to 29 ml/min: 200 mg q72h</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>&lt;15 ml/min and HD: 200 mg q96h</td>
</tr>
<tr>
<td>Epivir</td>
<td>Lamivudine</td>
<td>150 mg bid or 300 mg/d</td>
<td>30 to 49 ml/min: 150 mg/d</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>15 to 29 ml/min: 150 mg LD, 100 mg/d</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>5 to 14 ml/min: 150 LD, 50 mg/d</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>&lt;5 ml/min: 50 mg LD, 25 mg/d</td>
</tr>
<tr>
<td>Hivid</td>
<td>Zalcitabine</td>
<td>0.75 mg tid</td>
<td>10 to 40 ml/min: 0.75 mg q12h</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>&lt;10 ml/min: 0.75 mg q24h</td>
</tr>
<tr>
<td>Retrovir</td>
<td>Zidovudine</td>
<td>300 mg bid or 200 mg tid</td>
<td>HD or PD: 100 mg q6–8h</td>
</tr>
<tr>
<td>Videx, Videx EC</td>
<td>Didanosine</td>
<td>≥ 60 kg: 200 mg bid</td>
<td>30 to 59 ml/min: &gt;60 kg: 100 q12h or EC 200/d</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>&lt;60 kg: 75 q12h or EC 125/d</td>
</tr>
<tr>
<td></td>
<td></td>
<td>≤ 60 kg: 125 mg bid</td>
<td>10 to 29 ml/min: &gt;60 kg: 150/d or EC 125 mg/d</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>&lt;60 kg: 125/d or EC 125/d</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>&lt;10 ml/min, HD: &gt;60 kg: 100/d or EC 125 mg/d</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>&lt;60 kg: 75/d or EC: Avoid</td>
</tr>
<tr>
<td>Viread</td>
<td>Tenofovir</td>
<td>300 mg/d</td>
<td>30 to 49 ml/min: 300 mg q48h</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>10 to 29 ml/min: 300 mg q24h</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>&lt;10 ml/min without HD: No data</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>HD: 300 mg every 7 d</td>
</tr>
<tr>
<td>Ziagen</td>
<td>Abacavir</td>
<td>300 mg bid or 600 mg/d</td>
<td>No dosage adjustment</td>
</tr>
<tr>
<td>Zerit</td>
<td>Stavudine</td>
<td>≥ 60 kg: 40 mg q12h</td>
<td>26 to 50 ml/min: &gt;60 kg: 20 mg q12h</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>&lt;60 kg: 15 mg q12h</td>
</tr>
<tr>
<td></td>
<td></td>
<td>≤ 60 kg: 30 mg q12h</td>
<td>10 to 25 ml/min, HD (administer after HD):</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>≥60 kg: 20 mg/d</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>&lt;60 kg: 15 mg/d</td>
</tr>
</tbody>
</table>

*For guidance with dosing antiretroviral combinations and dosing in HAART-experienced patients, refer to individual package inserts. LD, loading dose; HD, hemodialysis; PD, peritoneal dialysis; EC, enteric coated.*

**Table 3. Nucleoside reverse transcriptase inhibitor fixed-dose combinations**

<table>
<thead>
<tr>
<th>Brand Name</th>
<th>Generic Name</th>
<th>Usual Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Combivir</td>
<td>Lamivudine, Zidovudine</td>
<td>One tablet bid</td>
</tr>
<tr>
<td>Trizivir</td>
<td>Abacavir, Lamivudine, Zidovudine</td>
<td>One tablet bid</td>
</tr>
<tr>
<td>Truvada b</td>
<td>Emtricitabine, Tenofovir</td>
<td>One tablet daily</td>
</tr>
<tr>
<td>Epizicom</td>
<td>Abacavir, Lamivudine</td>
<td>One tablet daily</td>
</tr>
</tbody>
</table>

*Avoid with GFR <50 ml/min; substitute individual components at appropriate dose. For guidance with dosing antiretroviral combinations and dosing in HAART-experienced patients, refer to individual package inserts. 
*bCan be administered if CrCl 30 to 49 ml/min q48 h; avoid if CrCl <30 ml/min and HD.*

**PI**

PI are metabolized primarily in the liver. Urinary excretion accounts for approximately 10% of parent drug clearance for indinavir and 5% or less for the other drugs in this class. The majority of PI have large volumes of distribution and are highly protein bound; indinavir is approximately 60% protein bound, and the other drugs in this class are 90% to >98% protein bound (15). None of the currently available PI requires dose adjustment for patients with impaired kidney function (Table 1).

Although studied only in a small numbers of patients, the PI are not cleared to any significant extent by hemodialysis and peritoneal dialysis (16–21), although there are conflicting reports about removal of nelfinavir by hemodialysis (22,23).

**NRTI**

All of the NRTI except abacavir (24) require dosage adjustment in patients with impaired kidney function and in patients...
who are on hemodialysis; these drugs should be dosed after dialysis (Table 2). These are small molecules with volumes of distribution of 0.5 to 1.9 L/kg and low protein binding (4 to 38%). Abacavir and to a somewhat lesser extent zidovudine are metabolized in the liver to inactive metabolites. Urinary excretion of parent drug is 1% for abacavir, 15 to 20% for zidovudine, and 30 to 70% for the other NRTI. For many of the NRTI, urinary excretion is by both filtration and tubular secretion, so other drugs such as cimetidine and trimethoprim can reduce their elimination (25). Two of the newer agents of this class, tenofovir and emtricitabine, are discussed below. Dosing for the others is shown in Table 2; further information, including information about clearance by dialysis, can be found elsewhere (11–13).

Tenofovir disoproxil fumarate is a pro-drug of the active agent tenofovir. Tenofovir primarily undergoes renal elimination, with 70% of an intravenous dose and approximately 30 to 35% with chronic oral dosing appearing in the urine, mostly as parent drug, by a combination of filtration and tubular secretion. It is approximately 1% bound to plasma proteins (26,27). Experience in patients with reduced GFR is limited, but current recommendations are that dosing adjustments be made in patients with CrCl <50 ml/min (Table 2). There is significant clearance with hemodialysis, so the dose of tenofovir should be given after dialysis or on a nondialysis day (28). Removal by peritoneal dialysis has not been studied.

Emtricitabine is also eliminated through glomerular filtration and active tubular secretion, with urinary excretion accounting for approximately 85% of an administered dose, mostly as parent drug (29). There is minimal protein binding (<4%). Dosage adjustment in renal impairment is necessary (Table 2). Hemodialysis removes approximately 30% of a dose, so the dose should be administered after dialysis on dialysis days.

In the past few years, the availability of combinations of two or three NRTI has significantly improved patient compliance and decreased pill burden. Because many of the individual medications require adjustment with renal impairment, fixed dose combinations should not be administered in patients with significantly reduced GFR. Instead, the medications should be administered separately so that appropriate dosage adjustments are made for each individual agent. Epzicom (lamivudine/abacavir), Trizivir (abacavir/lamivudine/zidovudine), and Combivir (lamivudine/zidovudine) should not be administered with CrCl <50 ml/min. Truvada (emtricitabine/tenofovir) requires an interval change from daily to every 48 h with CrCl of 30 to 49 ml/min and should be avoided in patients who are on dialysis or have CrCl <30 ml/min (Table 3).

NNRTI

The NNRTI primarily undergo hepatic metabolism, with little urinary excretion of parent drug. Nevirapine is approximately 60% protein bound, whereas the protein binding of delavirdine and efavirenz is 98 to 99% (30). Nevirapine, with <3% urinary excretion of parent drug, does not require dose adjustment in patients with impaired kidney function, although because there is some clearance by hemodialysis, the dose should be given after dialysis (21,31). Nevirapine is also removed to some extent by peritoneal dialysis, with peritoneal dialysis fluid concentrations reaching approximately half of the plasma concentration (17,20). It is not clear whether this necessitates a dosage adjustment, though, because there does not seem to be an effect on trough plasma levels (Table 4).

Efavirenz has not been studied in patients who have reduced GFR and are not on dialysis, but dosage adjustment is probably not needed. Less than 1% of parent drug is excreted in the urine. The clearance of efavirenz by hemodialysis and peritoneal dialysis is low, so dose adjustment or change in the timing of administration in patients who are on dialysis should not be necessary (32,33). Delavirdine has not been studied in patients with reduced GFR or in those who are on dialysis, but it is probably not necessary to make dose adjustments. Less than 5% of a dose is excreted unchanged in the urine.

Table 4. Non-nucleoside reverse transcriptase inhibitors and fusion inhibitorsa

<table>
<thead>
<tr>
<th>Non-nucleoside reverse transcriptase inhibitors</th>
<th>Generic Name</th>
<th>Usual Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Viramune</td>
<td>Nevirapine</td>
<td>Initial: 200 mg/d × 14 d; maintenance: 200 mg bid</td>
</tr>
<tr>
<td>Rescriptor</td>
<td>Delavirdine</td>
<td>400 mg tid</td>
</tr>
<tr>
<td>Sustiva</td>
<td>Efavirenz</td>
<td>600 mg/d</td>
</tr>
<tr>
<td>Fusion inhibitor</td>
<td>Fuzeon</td>
<td>90 mg bid</td>
</tr>
</tbody>
</table>

*No dose adjustments are necessary for patients who have reduced GFR or who are on dialysis. For guidance with dosing antiretroviral combinations and dosing in HAART-experienced patients, refer to individual package inserts.

Entry/Fusion Inhibitors

Enfuvirtide, the only currently available entry/fusion inhibitor, inhibits the fusion of the HIV capsid with the cell membrane of CD4 lymphocytes so that the virus cannot penetrate the cell. Enfuvirtide is injected subcutaneously and has high protein binding (approximately 92%). The drug, a peptide, is partially converted to an inactive deamidated metabolite, which, along with the parent drug, undergoes catabolism to amino acid residues (34). Detailed pharmacokinetic studies in patients with impaired renal function have not been performed.
but clearance seems not to be altered (35). It is not likely that there is significant clearance by dialysis (Table 4).

**Drug–Drug Interactions Involving Antiretroviral Agents**

With HAART, multiple medications are prescribed for treatment of HIV infection. Patients are also prescribed other medications for prevention or treatment of opportunistic infections and for management of their other medical conditions. Therefore, the potential for drug–drug interactions is significant. The PI and NNRTI are metabolized by the cytochrome P450 (CYP450) enzyme system, primarily through the CYP3A4 isoform, which is present in the liver and small intestine. Most drug–drug interactions involving PI and NNRTI occur as the result of induction or inhibition of the CYP450 system (36,37).

Some of these interactions have been used constructively, such as using subtherapeutic doses of ritonavir to “boost” the pharmacologic effect of co-administered HAART medications (38). Also important in the elimination of certain drugs is P-glycoprotein (P-gp), an ATP-dependent transporter located in the apical membrane of mucosal cells of the gastrointestinal tract, hepatic biliary canaliculi, and proximal tubule epithelial cells. P-gp is involved in the efflux from cell interior into the intestinal and nephron lumen of a variety of drugs, including PI. The CYP450 system and P-gp are also involved in the metabolism and elimination of glucocorticosteroids, cyclosporine, tacrolimus, and sirolimus (39). Thus, interactions between HAART agents and these other drugs need to be considered in the HIV-infected renal transplant recipient. Mycophenolate mofetil and azathioprine are not metabolized by the CYP450 system or transported by P-gp, so interactions with HAART medications are less of an issue.

Awareness of interactions between HAART and over-the-counter or herbal medications is also important, as highlighted by St. John’s wort (*Hypericum perforatum*). This herbal preparation induces several CYP450 isoenzymes and P-gp (40) and can lead to reduction in the concentration and effect of PI and NNRTI (41,42). Its use is contraindicated or cautioned against in patients who are taking PI and NNRTI, and we recommend avoiding this agent entirely.

For greatest safety, the package insert for each medication should be consulted for a detailed list of drug interactions. A detailed and updated list of such interactions can also be found at http://www.hiv-druginteractions.org and http://aidsinfo.nih.gov/guidelines/adult/AA_040705.pdf.

**PI**

All of the PI are substrates and to varying degrees inhibitors of the CYP450 3A4 isoenzyme. Some also induce certain CYP450 isoenzymes, whereas others inhibit other CYP450 enzymes. Because of these effects on the CYP450 system, many drug–drug interactions between PI and other medications have been demonstrated (36,37); some that are of particular interest to nephrologists are shown in Table 5. PI should be avoided

<table>
<thead>
<tr>
<th>Concomitant Medication</th>
<th>Clinical Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anticoagulant: Warfarin</td>
<td>Concentrations of warfarin may be affected; monitor International Normalized Ratio (INR)</td>
</tr>
<tr>
<td>Anticonvulsants: Carbamazepine, phenobarbital, phenytoin</td>
<td>Increased serum concentrations; monitor for toxicity</td>
</tr>
<tr>
<td>Antifungals: Ketoconazole,itraconazole, voriconazole</td>
<td>Increased serum concentrations of CCB; clinical monitoring of patients warranted; increased bepridil concentrations have been associated with life-threatening arrhythmias</td>
</tr>
<tr>
<td>Calcium channel blockers (CCB): Diltiazem, felodipine, nifedipine, nicardipine, verapamil, amlodipine, isradipine, bepridil</td>
<td>Increased statin concentrations; potential for myopathy, rhabdomyolysis; pravastatin, fluvastatin, rosuvastatin preferred</td>
</tr>
<tr>
<td>HMG-CoA reductase inhibitors (statins): Lovastatin, simvastatin, atorvastatin</td>
<td>Increased immunosuppressive concentrations; may need to initiate lower doses and monitor levels</td>
</tr>
<tr>
<td>Immunosuppressive: Cyclosporine, tacrolimus, sirolimus</td>
<td>Decreased methadone concentrations; may require dosage increase</td>
</tr>
<tr>
<td>Opioids: Methadone</td>
<td>Increased PDE5 concentrations; monitor for toxicity. Reduce PDE5 dosages and extend frequencies</td>
</tr>
<tr>
<td>PDE5 inhibitors: Sildenafil, vardenafil, tadalaft</td>
<td>Increased tricyclic antidepressants concentrations; monitor for toxicity</td>
</tr>
</tbody>
</table>

*PDE5, phosphodiesterase type 5. Refer to specific package inserts for more detailed information on these and other drug interactions.*
with simvastatin and lovastatin and have drug–drug interactions with other statins that require reduced doses and careful monitoring because of the potential for development of myopathy and rhabdomyolysis (43–46). Amiodarone and certain other antiarrhythmic agents are contraindicated with ritonavir and indinavir. Proton pump inhibitors should be avoided with atazanavir because of reductions in its serum concentration.

Many of the PI have bidirectional interactions with azole antifungal agents or have the potential for such interactions. Phenytoin, carbamazepine, and phenobarbital also interact bidirectionally with the PI; they can decrease PI levels, nelfinavir reduces phenytoin levels, and ritonavir increases carbamazepine levels (47).

Calcium channel blockers are also metabolized by the CYP3A4 isoenzyme (48). Symptomatic hypotension has been reported when these drugs are combined with PI (49). Plasma concentrations of β blockers such as metoprolol, pindolol, and timolol are increased by ritonavir (48). Ritonavir also reduces both renal and nonrenal clearance of digoxin (50). Antacids and H2-receptor agonists may affect the absorption of PI and so should be separated by 12 h to prevent decreased PI levels. Because PI increase blood levels of sildenafil, vardenafil, and tadalafil, initial doses should be reduced and patients should be monitored carefully for side effects.

Glucocorticoids are substrates of CYP3A4 and P-gp. PI inhibit metabolism of glucocorticoids, increasing their plasma concentrations and clinical effects, so doses may need to be reduced accordingly (36,51). Inhibition of the metabolism of inhaled glucocorticoids by ritonavir has resulted in Cushing’s syndrome and adrenal suppression (52,53). Glucocorticoids may also be inducers of CYP3A4, reducing plasma levels of co-administered PI. Cyclosporine, tacrolimus, and sirolimus are substrates and inhibitors of CYP3A4 and P-gp. Administration of these drugs with PI has the potential to delay elimination and markedly increase blood concentrations of both drugs (54–58). Bioavailability is also increased. Addition of saquinavir tripled the previously stable cyclosporine trough level in one renal transplant patient, in whom a 50% reduction in cyclosporine dose produced concentrations of cyclosporine similar to those seen on the higher dose without saquinavir (58). Reduction of the daily cyclosporine dose by 5 to 20% of the original dose was necessary after lopinavir/ritonavir was added in patients who were already taking cyclosporine (59). Use of lopinavir/ritonavir allowed dosing with 0.5 to 1 mg of tacrolimus weekly to maintain desired plasma levels (60). Use of nelfinavir has also necessitated marked reduction in the dose of tacrolimus (61). In five liver and kidney transplant recipients who were taking PI (nelfinavir or indinavir), cyclosporine levels increased progressively over time, even as the cyclosporine dose was decreased by 85% (62). Because there is a great deal of interindividual variability, therapeutic concentrations of immunosuppressants such as cyclosporine, tacrolimus, and sirolimus should be monitored routinely, with dosage adjustments made as necessary.

**NNRTI**

NNRTI also are metabolized extensively by the CYP450 system, including CYP3A4 and other isoenzymes. Nevirapine is an inducer, delavirdine is a potent inhibitor, and efavirenz can both inhibit and induce CYP3A4 and other isoenzymes (63). These effects lead to important and at times unpredictable interactions with PI and other NNRTI (30), as well as other drugs that may be prescribed or monitored by nephrologists (Table 6).

Fluconazole can lead to a doubling of nevirapine levels but does not seem to affect delavirdine or efavirenz in this way. There are interactions between NNRTI and the other azole antifungal agents as well. Efavirenz reduces levels of simvastatin and atorvastatin, whereas delavirdine has the potential to increase significantly statin levels and their toxicity (64,65). Use of carbamazepine, phenytoin, and phenobarbital is contraindicated with delavirdine because of marked reduction in delavirdine levels. Plasma concentrations, clinical effects, and toxicities of calcium channel blockers, antiarrhythmics, warfarin, sildenafil, vardenafil, and tadalafil should be monitored when patients receive concomitant therapy with an NNRTI.

Delavirdine inhibits metabolism of glucocorticoids and increases their blood levels, whereas efavirenz and nevirapine reduce glucocorticoid levels. Conversely, glucocorticoids have the potential to decrease the levels of the NNRTI because they induce CYP3A4 (36). In contrast to PI, NNRTI seem to have less of an effect on cyclosporine pharmacokinetics (62), although in one renal transplant recipient, efavirenz reduced cyclosporine levels by approximately 75% (66). Delavirdine increases levels of sirolimus and tacrolimus, so lower doses should be initiated and levels should be monitored (36).

**NRTI and Fusion Inhibitors**

Because these drugs do not undergo significant metabolism by CYP450 enzymes, interactions related to this system do not occur. However, some of the NRTI undergo hepatic metabolism by other mechanisms, so interactions between different antiretroviral agents can occur (67).

NRTI do not have specific pharmacokinetic interactions with transplant immunosuppressive medications. The active metabolite of mycophenolate mofetil, mycophenolic acid, does seem to potentiate the *in vitro* antiviral activity of abacavir, ddI, and tenofovir (68).

The entry/fusion inhibitor enfuvirtide is not metabolized through the CYP450 system and has little or no effect on other drugs that are metabolized by related enzymes. Significant drug–drug interactions with enfuvirtide have not been identified (34).

**Renal Toxicity of Antiretroviral Agents**

In a recent cohort study of ambulatory HIV-infected patients, acute renal failure (ARF) occurred in nearly 10% of patients, with an incidence rate of 5.9 episodes of ARF per 100 person-years (69). Medications were associated with approximately one third of all episodes; amphotericin B and various antibiotics were most commonly implicated. Among antiretroviral medi-
cations, tenofovir and indinavir are most commonly associated with nephrotoxicity (70–72).

Tenofovir (tenofovir disoproxil fumarate) has been associated with development of ARF and dysfunction of proximal and distal tubules. Lactic acidosis, which can occur with tenofovir and other NRTI, is discussed below. Verhelst et al. (73) first described a patient who was treated with tenofovir and developed reversible Fanconi syndrome, nephrogenic diabetes insipidus, and ARF. Renal biopsy demonstrated cytoplasmic vacuolization, apical localization of nuclei, and reduction of the brush border on proximal tubule epithelial cells. Fanconi syndrome and ARF also had been described previously in animal studies. Other cases of reversible tubular dysfunction, including Fanconi syndrome, nephrogenic diabetes insipidus, and ARF, have also been reported, with onset usually within 5 to 12 mo after starting therapy and recovery usually occurring within a few months after tenofovir discontinuation (74–77). In some of these patients, kidney biopsies showed similar findings as well as evidence of acute tubular necrosis, interstitial infiltrates, fibrosis, and edema, with cytopathic changes involving proximal and distal tubules. Glomeruli and blood vessels generally have not been involved. Low-grade proteinuria has been described, but nephrotic-range proteinuria is rare.

Most patients with tenofovir-related renal dysfunction were also receiving ritonavir and other agents. Tenofovir is taken up into renal epithelial cells by basolateral membrane human organic anion transporters, then secreted into the urine across the apical membrane by transporters called multidrug resistance–associated proteins (70). Other transporters may also be involved. Concomitant use of ritonavir (alone or in combination with lopinavir or other PI) raises plasma concentrations of tenofovir and may increase the risk for renal dysfunction as a result of inhibition by ritonavir of apical membrane transporters and increased intracellular accumulation of tenofovir. Although the actual mechanism of toxicity remains to be determined, close monitoring of patients who are taking this combination of medications is recommended, with careful attention to proper dosing for the level of GFR. Although it has been reported that the incidence of ARF is not higher with tenofovir compared with other antiretrovirals and that most patients who develop ARF on tenofovir have other explanations for ARF (78), there is sufficient concern that there is some risk for developing reduced kidney function that patients who receive tenofovir should have assessment of renal function, serum phosphorus concentration, and urinalysis at least biannually (13,79). Glucosuria and hypophosphatemia tend to be early manifestations of tenofovir-induced injury and should prompt discontinuation. Serum creatinine levels return toward baseline levels and tubular abnormalities resolve usually within 1 to 2 mo after tenofovir is stopped, although serum creatinine levels remain above baseline levels in some patients (76,80). In one patient with ARF attributed to tenofovir, kidney function did not improve and chronic dialysis was required (81).

Indinavir has been associated with crystalluria, nephrolithiasis, and obstructive ARF (82–85). Asymptomatic crystalluria occurs in up to two thirds of treated patients; pyuria, microscopic hematuria, and low-grade proteinuria are also seen. Indinavir crystalluria and nephrolithiasis can present with back or flank pain, dysuria, urinary urgency, and gross hematuria.

<table>
<thead>
<tr>
<th>Concomitant Medication</th>
<th>Clinical Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antiarrhythmics: Amiodarone, quinidine, lidocaine, flecainide, propafenone</td>
<td>Increased antiarrhythmic concentrations</td>
</tr>
<tr>
<td>Anticoagulant: Warfarin</td>
<td>Increased warfarin concentrations; monitor INR and initiate with lower doses</td>
</tr>
<tr>
<td>Anticonvulsants: Carbamazepine, phenobarbital, phenytoin</td>
<td>May alter serum concentrations</td>
</tr>
<tr>
<td>Calcium channel blockers (CCB): Diltiazem, felodipine, nifedipine, nicardipine, verapamil, amlodipine, isradipine, bepridil</td>
<td>Increased serum concentrations of CCB; monitor for changes in efficacy or development of toxicity; increased bepridil concentrations may be associated with life threatening arrhythmias</td>
</tr>
<tr>
<td>HMG Co-A reductase inhibitors (statins): Lovastatin, simvastatin, atorvastatin</td>
<td>Potential for myopathy, rhabdomyolysis; consider pravastatin, rosuvastatin, fluvastatin (low doses)</td>
</tr>
<tr>
<td>Immunosuppressives: Cyclosporine, tacrolimus, sirolimus</td>
<td>Variable effects on immunosuppressive concentrations depending on NNRTI; monitor levels</td>
</tr>
<tr>
<td>Opioids: Methadone</td>
<td>Increased methadone concentrations; may require initiation of lower dose</td>
</tr>
<tr>
<td>PDE5 inhibitors: Sildenafil, vardenafil, tadalafil</td>
<td>Increased PDE5 concentrations; monitor for toxicity; reduce PDE5 dosages and extend frequencies</td>
</tr>
</tbody>
</table>

*aRefer to specific package inserts for more detailed information on these and other drug interactions. NNRTI, non-nucleoside reverse transcriptase inhibitor.
Elevated serum creatinine levels have been noted in nearly 20% of treated patients, most with concomitant pyuria (86,87). Kopp et al. (85) described two overlapping presentations in patients who were treated with indinavir. A presumed interstitial nephritis, defined not by renal biopsy but by the presence of either an elevated serum creatinine without apparent cause or urinary cellular casts with red blood cells, white blood cells, or tubular epithelial cells, was seen in 61% of patients. Histopathologic documentation of an acute interstitial nephritis associated with intratubular indinavir crystals has been reported by others (88). The pyuria and azotemia resolved in those who discontinued indinavir. Urothelial inflammation, thought to be due to indinavir crystals’ irritating urinary tract transitional epithelial cells and causing clusters of these cells to appear in the urine, was seen in 74% of patients.

Symptomatic crystalluria or nephrolithiasis can develop anytime after drug initiation and has been reported in as many as 33% of patients who are on chronic therapy. Obstructive uropathy with indinavir may be mild and resolve spontaneously or be severe, with bilateral obstruction requiring urologic intervention. Acute or subacute ARF without crystalluria with renal biopsy findings of intratubular and intracellular crystals with chronic interstitial nephritis, interstitial fibrosis, tubular atrophy, and multinucleated histiocytes has also been described (88,89).

Indinavir is metabolized primarily in the liver, but renal excretion of parent drug accounts for approximately 10% of a dose. Indinavir is highly soluble in acidic urine (100 mg/ml at pH 3.5) but relatively insoluble in more alkaline urine (0.3 mg/ml at pH 5.0, 0.035 mg/ml at pH 6.0, and 0.02 mg/ml at pH 7.0), predisposing to the development of crystals at typical urine pH levels (90). Crystals of varying shapes have been described and are more common in urine with pH ≥6 (83,84,91). Urinary stones are composed primarily of indinavir monohydrate; calcium oxalate and phosphate as well as indinavir metabolites may also be present (83,92). Most are radiolucent and are not detectable with plain radiographs.

It is recommended that patients who start on indinavir be monitored periodically during the first 6 mo of therapy, then biannually thereafter for changes in renal function and pyuria (13). Prevention of indinavir crystalluria and nephrolithiasis depends on maintenance of a daily fluid intake of at least 1.5 to 2 L. Urinary acidification, although theoretically of benefit, is not generally recommended. Patients who are treated with higher doses (e.g., ≥1000 mg twice daily) over longer periods of time are more likely to develop crystalluria; other risk factors are low lean body mass, co-infection with hepatitis B or C virus, and use of acyclovir or trimethoprim-sulfamethoxazole (84,86,93). In patients who develop indinavir-related nephrolithiasis, therapy usually can be resumed after resolution of the acute episode once adequate volume status is achieved.

Nephrolithiasis can also occur in HIV-infected patients for other reasons. In one retrospective review, only 28% of indinavir-treated patients with nephrolithiasis had indinavir-containing stones (94). The others and patients who were not taking indinavir had stones that contained calcium oxalate, ammonium acid urate, and uric acid, and some had various metabolic abnormalities, including hypocitraturia, hyperoxaluria, and hypercalciuria. Hypertension, renal atrophy, acute and chronic interstitial nephritis, and nephrogenic diabetes insipidus have also been described rarely with indinavir (85,95–98).

Other Antiretroviral Agents

PI. Renal calculi have been attributed to nelfinavir and saquinavir in single reports. Ritonavir has been associated with ARF in a few reports but without histopathologic characterization. ARF with interstitial lymphocytic and eosinophilic infiltrates was described recently in a patient who was taking atazanavir (99). Whereas some studies have specifically implicated PI in a possible association between HAART and hypertension (100,101), others have not found this (102–104). Amprenavir, fosamprenavir, and lopinavir have not been associated with any significant renal toxicity.

NRTI. There are rare reports of acute interstitial nephritis and proximal tubule dysfunction with abacavir and proximal tubular dysfunction and of Fanconi syndrome with ddI and stavudine/lamivudine; significant nephrotoxicity has not been reported with other NRTI.

Lactic Acidosis with NRTI. NRTI have been associated with development of disturbances in lactic acid homeostasis with presentations that range from asymptomatic chronic hyperlactatemia to acute, life-threatening lactic acidosis. Lactic acidosis was first described with didanosine and, even more common, zidovudine (105–107). Many of these patients also had massive hepatic steatosis and liver failure, and most died within a few days or weeks. Subsequent experience unveiled a wider range of lactate disorders associated with the NRTI as a class, as well as other disorders, including lipoatrophy, skeletal and cardiomyopathy, peripheral neuropathy, and pancreatitis. Although the exact pathophysiologic mechanisms remain to be proved, it is thought that these disorders are related at least in part to variable inhibition of mitochondrial DNA polymerase γ by intracellularly generated triphosphate metabolites of these drugs. Inhibition of hepatic mitochondrial DNA synthesis is thought to lead to impaired mitochondrial ATP synthesis, ATP depletion, and impaired oxidative phosphorylation with increased lactic acid production. Abnormalities in fatty-acid transport, oxidative damage, and apoptosis may also be involved (108–114).

Approximately 20 to 30% of patients who are treated with these drugs can be found to have asymptomatic hyperlactatemia (mildly elevated lactic acid levels, usually ≤2.5 mmol/L without acidemia) that typically develops after several months of therapy and may be transient (110,115,116). Severe lactic acidosis (elevated lactic acid levels >5 mmol/L with acidemia) is much rarer, occurring in 1.5 to 2.5% of patients, is usually preceded by fatigue, nausea, vomiting, anorexia, abdominal pain, and other systemic symptoms and is associated with a mortality rate of approximately 80%. Most patients with asymptomatic hyperlactatemia remain stable and do not develop symptomatic lactic acidosis. Stavudine and didanosine (alone or in combination) most commonly have been linked with hyperlactatemia and lactic acidosis in recent reports, although all of these agents have been implicated. Dual-NRTI
regimens including combinations of zidovudine or stavudine with didanosine, zalcitabine, or lamivudine seem to be associated with increased risk for lactic acidosis (114,115,117,118). Other possible risk factors that have been variably identified in some studies include longer duration of treatment, older age, female gender, pregnancy, hypertriglyceridemia, obesity, concomitant hepatitis C infection, use of ribavirin, impaired kidney function, and alcohol ingestion (9,115,116,118,119).

Routine monitoring for hyperlactatemia and lactic acidosis is not recommended, but lactate levels should be measured in patients who present with symptoms described above and who are found to have low bicarbonate levels, an elevated anion gap, or abnormal liver enzymes. More vigilant monitoring has also been suggested for patients with multiple risk factors (9,108,110,117,120–122). Treatment with NRTI should be terminated when symptomatic lactic acidosis develops but may be continued with chronic asymptomatic hyperlactatemia, particularly if lactate levels remain <5 mmol/L. Hyperlactatemia may persist for many weeks after NRTI are discontinued. Some patients tolerate resumption of NRTI therapy but require close monitoring (110). Intermittent hemodialysis or continuous renal replacement therapy and bicarbonate supplementation may be indicated in severe cases (107,123). Various therapies, including thiamine, L-carnitine, coenzyme Q10, and riboflavin, among others, have been tried but are of unproved efficacy (110–112,124).

**NNRTI.** Little in the way of renal toxicity has been reported with the NNRTI. Delavirdine was implicated in a case of ARF that was caused by rhabdomyolysis and was thought to be related to a drug interaction with atorvastatin (65). A single case of ARF with rash, eosinophilia, and systemic symptoms was described after initiation of a nevirapine-containing regimen (125). Efavirenz has not been associated with renal toxicity.

**Entry/Fusion Inhibitors.** A single case of membranoproliferative glomerulonephritis in a patient who was treated with enfuvirtide was reported, although because there was a history of proteinuria and hematuria and the patient was also treated with tenofovir, lamivudine, lopinavir-ritonavir, amprenavir, and efavirenz, a causative relationship with enfuvirtide is tenuous at best (126).

**Conclusions**

Advances in the pharmacologic management of HIV infection continue at a rapid pace. Although most antiretroviral agents are relatively free of renal toxicity, drug-related renal injury can occur and may need to be distinguished from progression of HIV-associated nephropathy or other HIV-related kidney diseases, kidney diseases caused by other infections (e.g., hepatitis C) or lymphoproliferative diseases, or kidney diseases unrelated to HIV infection and its treatment (71). As nephrologists see HIV-infected patients for both HIV- and non-HIV-related conditions, it is necessary to have an understanding of the pharmacokinetics of antiretroviral medications and how these medications need to be dosed in patients with impaired kidney function. It is also important for nephrologists to be aware of drug–drug interactions that occur between antiretroviral agents and other medications that they may prescribe.

This is going to become increasingly important as more HIV-infected patients undergo renal transplantation.

**References**


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